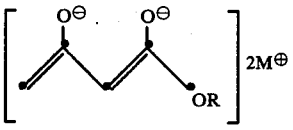
In words relative to the above diagram. L-aspartic acid 1 is esterified according to well known procedures. Typically 1 in a solvent such as benzene, toluene, chloroform or the like is treated with an esterifying agent such as benzyl alcohol, methanol, ethanol, isopropanol, or the like in the presence of p-toluene sulfonate acid, HCl, HBr, or the like at a temperature of from 0° to 110° C. for from 1 to 24 hours to achieve the desired establishment and hence protection of the carboxyl functions. The resulting species 2 in a solvent such as ether, THF, DME or the like is treated with trimethylchlorosilane, or the like followed by treatment with EtMgBr, MeMgI, ϕMgBr or the like at a temperature of from −40° to 50° C. for from 1 to 72 hours to provide azetidinone 3. Reduction of species 3 with a reducing agent such as $NaBH_4$, or the like in a solvent such as methanol, ethanol, isopropanol or the like at a temperature of from −10° to 40° C. for from 1 to 6 hours provides 4. (For purposes here, the symbols: Et, Me, ϕ, and iPr stand for: ethyl, methyl, phenyl and isopropyl, respectively.)

Treatment of 4 in a solvent such as methylene chloride, $CHCl_3$ or the like with methane sulfonyl chloride, methane sulfonic anhydride or the like in the presence of a base such as Et_3N, iPr_2NEt, or the like followed by treatment with a stoichiometric to 5 fold excess of sodium iodide in acetone yields 5 via 4a.

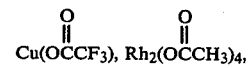
Treatment of 5 in a solvent such as THF, DME (dimethoxy ethane), ether, or the like with



at a temperature of from −78° to 25° C. for from 1 to 24 hours provides 6 wherein M is any compatible counter ion such as lithium, or other alkali metal; R is any conventional carboxyl protecting group such as t-butyl, benzyl, p-methoxybenzyl, or the like.

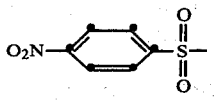
Diazotization of 6 is accomplished to provide 7 by treating 6 in a solvent such as CH_3CN, ϕCN (ϕ=phenyl), or the like at a temperature of from −20° to 25° C. for from 1 to 24 hours with an azide such as p-carboxybenzene sulfonyl azide, tosyl azide, or the like in the presence of a base such as Et_3N, iPr_2NEt or the like.

Cyclization of 7 to provide 8 is accomplished by treating 7 in a solvent such as benzene, toluene, octane or the like for from 1 to 5 hours at a temperature of from 50° to 110° C. in the presence of a catalyst such as bis-(acetylacetonato)CuII, [Cu(acac)$_2$],



or the like. Intermediate 8 is a mixture of keto-enol tautomers which exists primarily as the shown enol form.

Establishment of leaving group OR° is accomplished by treating intermediate enol 8 with tosyl anhydride, mesylanhydride, tosyl chloride, nosyl chloride, or the like in the presence of a base such as Et_3N, iPr_2NEt, or the like in a solvent such as CH_2Cl_2, $CHCl_3$, or the like at a temperature of from −30° to 25° C. for from 0.5 to 10 hours; thus relative to intermediate species 9 R° may for example be Ts(tosyl), CH_3SO_2—,



or the like.

Alkylation of 9 provides 10 on treating 9 in a solvent such as THF, DME, ether or the like with a strong base such as lithium diisopropylamide (LDA) Li-tetramethylpiperidide, KH or the like followed by treatment with a stoichiometric to 20 fold excess of acetaldehyde. Typically the reaction is conducted at a temperature of from −78° to 25° C.; and typically the acetaldehyde is added after 5 to 60 minutes after addition of the strong base; the alkylation reaction is completed in 0.1 to 1 hours. The aldol reaction provides a mixture of isomers which is conveniently separated by chromatography.

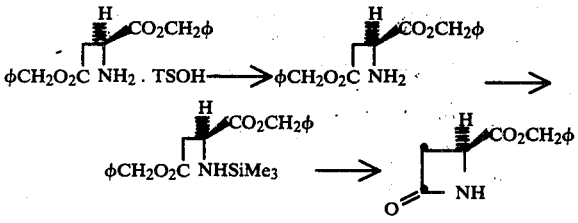
The aminoethylthio side chain is established by treating 11 in a solvent such as DMF, HMPA, DMSO or the like at a temperature of from −40° to 50° C. for from 1 to 72 hours with aminoethyl mercaptan or an acid addition salt in the presence of a base such as Et_3N, iPr_2NEt, pyridine or the like.

Deblocking of 11 provides I. Typically the deblocking is accomplished by hydrolysis or hydrogenation. When R is t-butyl, p-methoxybenzyl, benzhydryl or the like acid hydrolysis at a temperature of from 0° to 25° C. for from 0.1 to 5 hours is appropriate; when the carboxyl protecting group R is p-nitro benzyl, benzyl, or the like hydrogenation in a solvent such as dioxane, ethanol, or the like in the presence of a catalyst such as Pd/C, or the like under a hydrogen pressure of from 1 to 40 atmospheres for from 0.2 to 4 hours is appropriate.

The following Example illustrates but does not limit the process of the present invention. All temperatures are expressed in °C.

EXAMPLE 1

Preparation of Homothienamycin



Benzyl (S)-azetidin-2-one-4-carboxylate

To a 1000 ml separatory funnel are added dibenzyl (S)-aspartate p-toluenesulfonic acid salt (48.6 g, 0.1 mole), ice-cold diethyl ether (300 ml), ice-cold water (100 ml), and ice-cold saturated aqueous potassium carbonate (50 ml). The mixture is shaken vigorously and the layers are separated. The aqueous portion is extracted with more cold diethyl ether (2×100 ml). The combined ether solution is washed with brine, dried with magnesium sulfate, and evaporated under vacuum to provide dibenzyl (S)-aspartate (31.4 g, 0.1 mole) as a colorless liquid.

The dibenzyl (S)-aspartate in anhydrous diethyl ether (200 ml) is cooled in an ice-bath under a nitrogen atmo-